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Use of Positron Emission Tomography (PET): local practice and utilisation in preoperative staging of breast cancer

Editor's message

This issue intends to complement the "Hong Kong Breast Cancer Registry (HKBCR) Report No. 13" on the utilisation of Positron Emission Tomography (PET) in preoperative staging of breast cancer. Our findings showed that such new technology has an increased usage in preoperative staging over the past 15 years. With its high sensitivity, it was more commonly performed when the tumour was relatively big or of higher stage clinically. While no local guideline has been established for the use of PET in Hong Kong, HKBCR panel has proposed simple guidelines on the use of PET for breast cancer in the preoperative setting based on consistent findings from our registry and the clinical practice of a group of local experts.

Introduction

Breast cancer staging is a crucial diagnostic process that determines the extent of cancer's growth and metastasis. With an accurate pre-operative staging, a more suitable treatment option can be offered to patients. Nowadays, the utilisation of imaging procedures for staging has evolved from traditional methods, such as a combination of chest X-ray and ultrasound of abdomen, computed tomography (CT), bone scan, and magnetic resonance imaging (MRI), to more advanced hybrid molecular imaging techniques such as positron emission tomography (PET).

The technology

PET is a non-invasive diagnostic imaging technique that provides digital images of organ function with qualitative and quantitative metabolic information. The procedure involves an intravenous injection of a small amount of radiopharmaceuticals (so-called 'radiotracers') into the body whereby, following the biokinetics principle, they are physiologically and biochemically incorporated by the target organs or tissues. 2-^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG), a glucose analog, is the most commonly used radiotracer for tumour detection, including breast cancer, based on its role as a biomarker of abnormal glucose utilisation in malignant cells, a patho-biochemical process known as Warburg glycolysis.[1] ^{18}F-FDG is phosphorylated and trapped intracellularly in relation to the net, equilibrium rate of hexokinase enzyme activity, which forms the basis of PET imaging as a gauge of cellular growth and aggressiveness. In constellation with anatomical imaging, PET provides a "hybrid" or fused imaging technique with CT or MRI (PET/CT or PET/MRI) to give a co-registered metabolic-structural information, as well as with CT (PET/CT) for attenuation correlation.

Radiation exposure

Dual-modality PET/CT utilises 2 forms of ionizing radiation, gamma rays and X-rays. A patient's radiation exposure is measured in terms of effective dose (in units of mSv). The effective dose from a PET scan alone is modest and, when compared with radiotherapy, it is almost insignificant. Depending on the activity of the injected radiotracer, the effective dose of PET is typically 7-8 mSv for adults being administered with 370-400 MBq ^{18}F-FDG (adjusted according to body weight) and is the same whether a part of the body or the whole body is imaged.[2,3] The effective dose from CT is variable depending on the CT protocol, usually with an effective dose of ~7 mSv for a low dose non-contrast whole body CT.[2,3] In most international PET/CT centers, CT contrast is normally not necessary for oncologic PET studies requested for staging. The effective dose from a high resolution diagnostic CT scan alone with contrast can be as much as 30-40 mSv for a whole body CT evaluation.[3] However, low-dose radiation diagnostic procedures (<100 mSv) is universally considered safe by any international radiation rules and criteria.

International and local guidelines on the use of PET

While no local guideline has been established for the use of PET in Hong Kong, the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) recommended using PET scan when the standard staging studies or conventional methods are suspicious or inconclusive. NCCN further stated that PET scan might be beneficial in identifying tumours with nodal or metastatic involvement.

Objectives of the study

PET scan has been more available for breast cancer staging in the past decade. With the ability to demonstrate abnormal metabolic activities, PET is shown to be more sensitive in detecting axillary nodal and systemic metastases.[4] However, the cost, radiation exposure and possible false positive results might discourage physicians' usage, particularly in places, such as Hong Kong, where there are no local guidelines for the use of PET scan. Therefore, there is a need to determine the role of PET scan in the staging of breast cancer. The current study aims at investigating the usage pattern and the diagnostic and therapeutic impact of PET scan in pre-operative staging of breast cancer. We will also attempt to propose guidelines for the use of PET in preoperative settings.

Methodology

Records of female patients who had been diagnosed with breast cancer since 2006 were retrieved from the Hong Kong Breast Cancer Registry (HKBCR). HKBCR was established in 2007 by the Hong Kong Breast Cancer Foundation (HKBCF) and has since grown to become the most comprehensive and representative data collection and monitoring system for breast cancer in Hong Kong. HKBCF is the first non-profit charitable organisation in Hong Kong dedicated to mitigating the threat of breast cancer to the local community through education, patient support, research and advocacy.

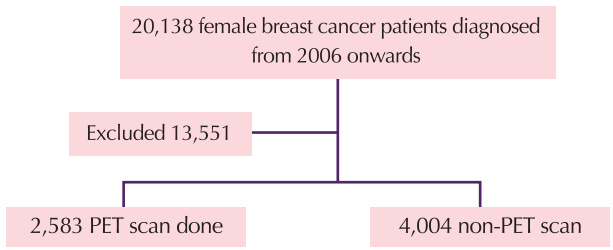
Among 20,138 patients, 11,376 patients with unknown cancer stage; 1,803 patients who have not received any adjuvant therapy; and 372 with bilateral disease were excluded. Hence, a total of 6,587 patients were included in this study. These patients were further stratified into two groups – with or without PET scan in preoperative assessment (see Figure 1).

The characteristics of the patients with and without pre-operative PET scan were compared. Results were tabulated with the sample size, percentages, sensitivity and specificity calculated in some subgroups to illustrate the accuracy of PET scan.

To propose guidelines in the use of PET in breast cancer in the preoperative setting, a short survey was sent out to members of the HKBCR Editorial

Group. The group comprises of 22 members with vast experience and interests in breast cancer management, including surgeons, oncologists, pathologists, radiologists and scientists. The survey consulted these experts whether they would recommend PET imaging to their patients in different clinical scenarios.

Figure 1: **Flowchart of recruitment**

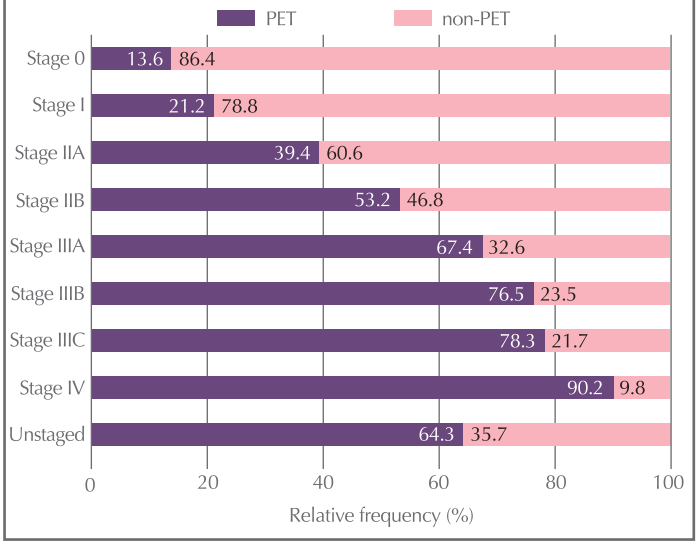


Results and Discussion

A. Pattern of use of PET scan

Figure 2 presents the distribution of patients with different pathological cancer stages with and without pre-operative PET scan. Most of our patients had lower stage breast cancer. PET scans were more commonly performed for patients with stage III (71.4%) and stage IV (90.2%), and less involved in early stage cancers, such as stage 0 (13.6%) and stage I (21.2%) cancers. Overall, the utilisation of PET among patients was 40%. This reflected a trend that physicians were more likely to recommend PET in higher stage disease because the sensitivity of PET has been reported to be associated with different tumour characteristics, particularly tumour size, which plays a significant part in determining the breast cancer stage.[5] This is also in line with the general recommendations by major international guidelines that PET may be more useful when nodal or metastatic disease were suspected.

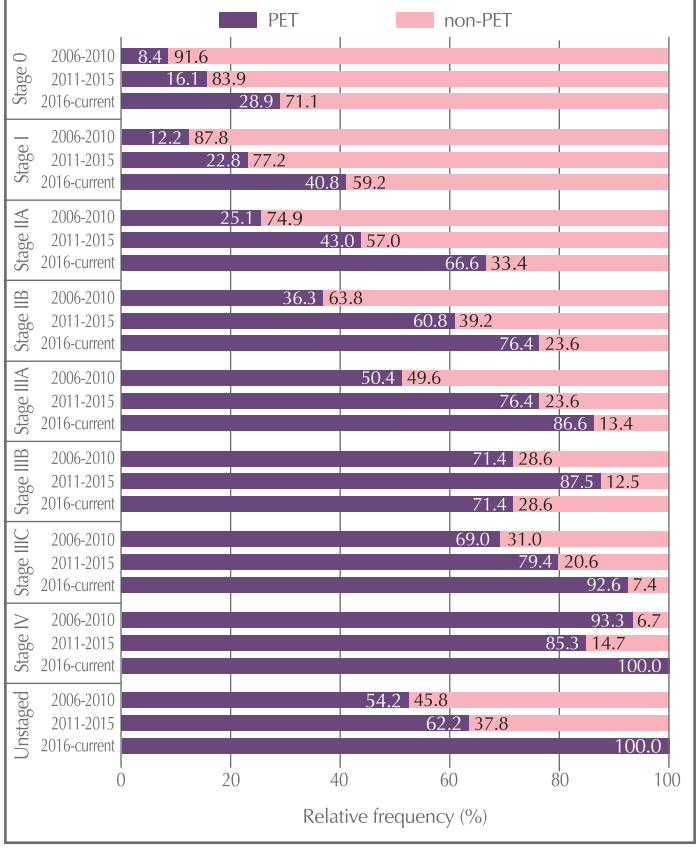
Figure 2: **Use of PET scan by cancer stage among patients (N=6,587)**



To examine the trend of usage over the past decades, Figure 3 further stratifies the results into three cohorts. The overall utilisation of PET scan has increased from 25.7% in 2006-2010 to 61.0% in the 2016-current cohort. In line with our previous findings, more patients with breast cancer of advanced stage had PET scan. It was also more often used on larger tumours, from around 70% in T3 to around 90% for T4 disease (while T describes the main tumour in terms of the size and extent of it), and the numbers have been increasing from the first to third cohort. About 70% of patients with node metastasis had PET in the preoperative setting. Of note, there was also an increasing percentage of patients with lower stage cancer using pre-operative PET scan (see Figure 3).

The trend largely reflected the increasing availability of PET facilities in Hong Kong. Over the past two decades, more PET scanning facilities were established both in the public and also the private sectors, and the service is more easily accessible.

Figure 3: **Use of PET scan by cancer stage among patients in three cohorts (N=6,587)**



Nevertheless, the common use of PET scan in diagnosing late stage breast cancer was consistent with previous studies.[6] The pattern of utilisation was also largely in line with the recommendations in major international guidelines from NCCN and ESMO, where PET imaging may be considered when the standard staging studies or conventional methods are suspicious or inconclusive; or when nodal or systemic metastases are suspected. Our results on tumour characteristics of patients who had or had not undertaken

Table 1: **Tumour characteristics of patients with and without PET scan**

	PET scan		non-PET scan	
	N	%	N	%
Subtype				
HR+ HER2-	1,582	37.6	2,631	62.4
HER2+ (HR+/-)	539	41.8	749	58.2
TNBC	286	44.6	355	55.4
Unclassified	122	46.6	140	53.4
Clinical tumour size (median)	2.30cm		1.80cm	
Clinical nodal stage				
N0	228	15.9	1,206	84.1
N1	143	69.1	64	30.9
N2 or above	41	69.5	18	30.5
Not known	2,117	45.0	2,587	55.0
Clinical metastasis				
M0	433	24.9	1,305	75.1
M1	20	95.2	1	4.8
Not known	2,076	44.7	2,569	55.3

PET scan showed that PET scan might be used more for tumours of larger size and when lymph nodes and metastasis were more likely involved (see Table 1).

An attempt was taken to examine the use of PET in different tumour characteristics other than size and stage. It had been demonstrated that FDG uptake was significantly higher in ductal breast cancer than in lobular cancer and FDG uptake correlated with proliferative activity assessed by Ki-67 immunostaining.[7] A significant correlation with the other prognostic markers, however, could not be demonstrated. From our data, we could not demonstrate any difference in utilisation among molecular subtypes – luminal (HR+ HER2-), HER2 positive (HER2+) or triple-negative (TNBC), despite that a higher sensitivity was expected in HER2+ and TNBC subtype.

B. Nodal involvement among PET and non-PET scan patients with both clinical and pathological cancer stage

In a smaller group of patients, clinical stage before operation and pathological stage after surgery were available, allowing us to look at the impact of staging with and without PET imaging. To examine the sensitivity and specificity of clinical staging using PET scan, the clinical and pathological nodal involvement among the two groups of patients was investigated. While the sensitivity among patients who had PET scan was much higher (70.3%) than whom did not (30.4%), the specificity was numerically slightly higher in patients without undergoing PET scan (99.3% compared to 91.3% in PET group). Such high sensitivity suggested that PET scan was more likely to pick up nodal and distant metastases, thereby providing a more accurate breast cancer staging in determining the treatment options and recovery of patients.[8] Of note, the sensitivity and specificity could be influenced by several factors such as breast infection, fat necrosis and lactation.[9]

In addition, adopting PET scan preoperatively may avoid unnecessary sentinel lymph node biopsy (SNB) if positive nodal metastases were diagnosed preoperatively. While false positive detection of lymph nodes could lead to unnecessary axillary dissection (AD), positive axillary PET scan might enhance the accuracy of SNB and reduce the risk of false negative SNB. PET scan could lower the chance of performing unnecessary SNB as the condition of metastasis can be reviewed more accurately.[10] Although subsequent adjuvant treatment would be determined by the final pathological stage, detection of nodal metastases before surgery might allow the surgeon to proceed to AD without the need for SNB in the theatre. Apart from the axillary surgical intervention, the identification of regional nodal involvement (i.e., axilla and/or supraclavicular regions) before the primary breast cancer surgery can also assist the decision making regarding the application of (neo)adjuvant oncological therapy before surgery. The post-surgical pathological information can provide more realistic prognostic information for certain breast cancer subtypes, which can affect the post-surgical adjuvant oncological treatment decisions.

With regards to the sensitivity and specificity of clinical staging with PET in different molecular subtypes (Table 1), we explored the relationship between the accuracy of PET scan, tumour size and molecular subtypes by stratifying the groups based on certain tumour subtypes (Table 2) and tumour size (Table 3). PET in general improved the sensitivity especially in HER2+ or TNBC tumours, but the specificity was slightly lower.

Table 3 shows the tumour size in true-positive (TP), false-positive (FP), false-negative (FN), and true-negative (TN) groups of the clinical staging with and without PET scan. It was found that the tumour sizes were similar in these subtypes between specific PET groups, indicating that the observation on molecular subtypes and the accuracy of PET scan were not related to tumour size.

Table 2: **Preoperative staging sensitivity and specificity in molecular subtypes among patients who had or had not undergone PET scan**

	Sensitivity (%)		Specificity (%)	
	PET	Non-PET	PET	Non-PET
HR+ HER2-	67.4	28.3	95.0	99.1
HER2+	74.1	37.5	92.9	99.4
TNBC	76.7	41.7	80.0	100.0

Table 3: **Clinical tumour size among patients with different molecular subtypes**

	TP (median ±*SD*)		FP (median ±*SD*)		FN (median ±*SD*)		TN (median ±*SD*)	
	PET	Non-PET	PET	Non-PET	PET	Non-PET	PET	Non-PET
HR+ HER2-	2.50± 1.63	2.10± 0.94	3.35± 1.49	2.50± 6.20	2.00 ± 1.10	1.90± 0.84	2.10± 1.43	1.50± 0.96
HER2+ (HR+/-)	2.63± 1.61	2.80± 1.52	3.50#	1.50#	2.50± 1.21	2.05± 0.87	2.50± 0.96	1.90± 1.02
TNBC	2.25± 2.95	1.95± 1.47	4.05± 1.90	—	3.00± 0.78	1.85± 0.45	1.70± 1.20	1.90± 0.77

Note: # only one case in this group

C. Practice in Hong Kong and the recommendations on the use of PET scan by HKBCR panel

In view of the utilisation pattern of PET scan revealed and discussed earlier, a short survey was conducted to learn further about the practice in clinical settings. The survey employed 26 items to access the use of PET scan in institutions of Hong Kong. The specialists were asked if PET scan would be recommended for patients with breast disease under various conditions regarding tumour stages, nodal status, molecular subtypes, breast symptoms and treatment plans. A total of 15 responses were received from the 22 members.

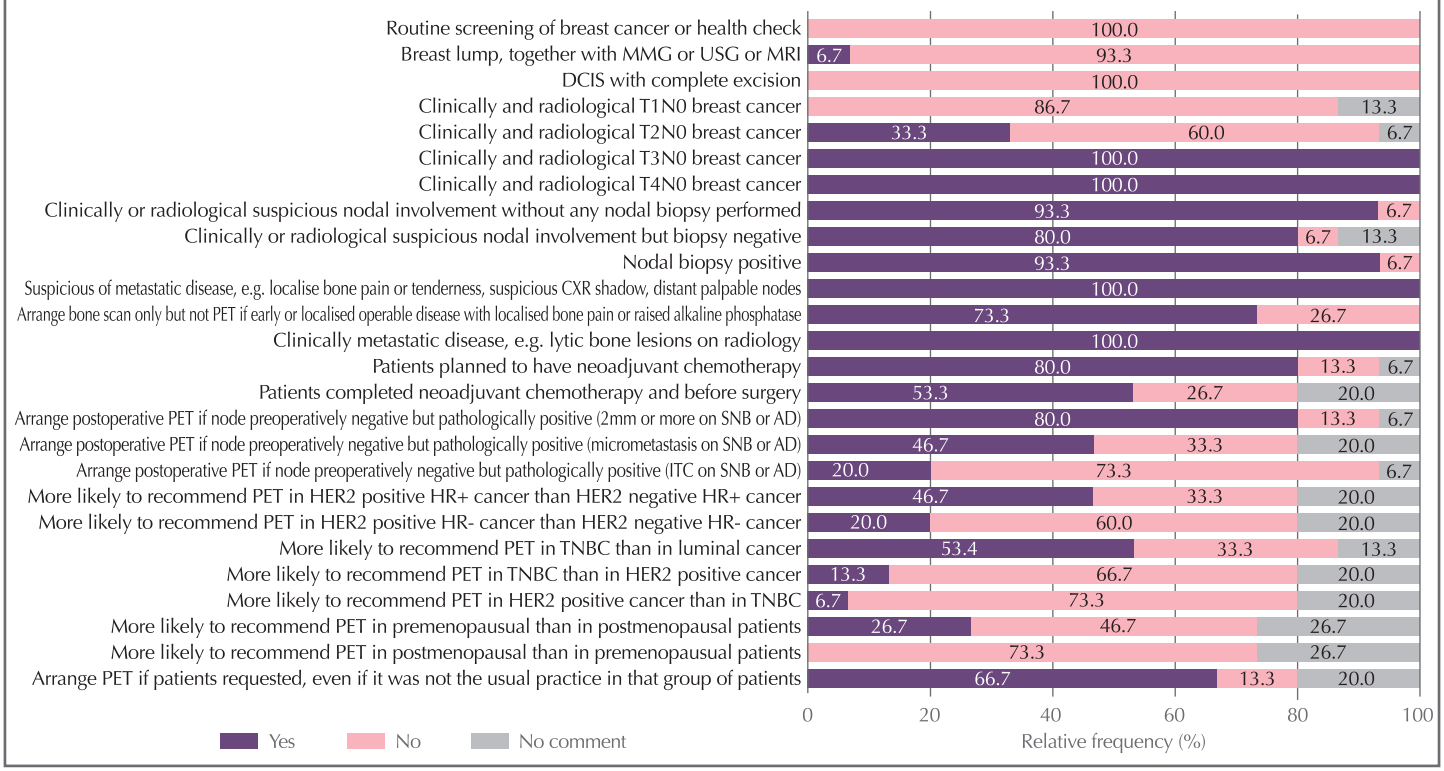
Figure 4 shows that the pattern of utilisation was comparable to what was found in the registry data analysis. PET scan was not suggested for breast cancer surveillance or stage 0 disease. It is highly recommended when nodal invasion was involved; larger tumour was detected (i.e., T3 and T4 breast cancer); and metastatic disease. Of note, PET scan could be arranged for the patient if they requested for one, even if it was not the usual practice in that group of patients (see Figure 5 for details).

Based on the results of this short survey, and the above analysis of the practices reflected in the registry, HKBCR panel has proposed some local

Figure 5: **Summary of the short survey on practice in clinical setting**

- **A.** Most respondents do not use PET in breast cancer screening and also clinically benign breast diseases
- **B.** Most respondents do not use PET in the initial assessment for clinically or pathologically stage 0 and I breast cancer
- **C.** Most respondents recommend PET for T3 or above tumours
- **D.** Most respondents recommend PET in patients with suspected or confirmed axillary node metastases, except in those with isolated tumour cells
- **E.** Most respondents recommend PET for suspected metastatic breast cancer
- **F.** For isolated bone symptoms without other evidence of metastases, isotope bone scan is an option
- **G.** Most respondents recommend PET before neoadjuvant chemotherapy, and many will consider PET after neoadjuvant chemotherapy and before surgery for response assessment
- **H.** Molecular subtypes do not seem to affect the use of PET nor the menopausal status of the patient
- **I.** Most will respect the choice of the patient if they would like to have PET as part of the staging

Figure 4: **Use of PET scan in different conditions (N=15)**



guidelines in the use of PET scan. In view of significantly higher radiation exposure, cost and availability of excellent alternatives of mammogram and ultrasonography, PET scan is not recommended for breast screening. It is also not recommended in clinically benign or early stage breast cancer. PET scan, however, should be considered for more advanced stage breast cancer with bigger tumour, suspected or confirmed nodal or metastatic disease. It is also recommended in the neoadjuvant chemotherapy setting (see Figure 6 for details).

Figure 6: **Proposed local guidelines for the use of PET**

1. PET is not a routine investigation in
   a. breast screening
   b. clinically benign breast diseases
   c. T0 and T1 breast cancer
2. PET should be considered in
   a. T3 or above breast cancer
   b. suspected or confirmed node positive cancer
   c. suspected or confirmed metastatic disease
   d. neoadjuvant chemotherapy

Limitations

Although HKBCR has the most comprehensive and representative data collection for breast cancer in Hong Kong, full staging information was not available for all the patients in the current study, which comprised of a small fraction of the subjects in the whole registry. Moreover, the reason for performing the PET scan and how that affected the final clinical staging was not available. Therefore, the results could be prone to bias. On the other hand, with follow-up analyses demonstrating consistent patterns over the years, and that our findings were in concordance with the practices in the survey, we were confident that our data was reflecting the true practice in the clinical settings. Future studies would be warranted to compare the findings on PET to other breast scanning modalities including mammography, ultrasonography, MRI and biopsy. Another topic of study would be to compare the clinical stage before and after a PET scan done in various clinical settings.

Conclusion

PET is a relatively new technology with high sensitivity and may pick up occult metastases in nodes as well as distant sites. However, some may consider it expensive and it is associated with radiation exposure. Therefore, it should be used only when indicated. Our data showed a trend in increased usage in preoperative staging over the past 15 years. It was more commonly performed when the tumour was relatively big or of higher stage clinically. It appears to have a high sensitivity and a reasonable specificity. However, our data did not reveal any obvious difference in its use for different molecular subtypes. The short survey conducted in a group of local experts on the use of PET showed that their practice was in line with our findings from the registry. HKBCR panel has proposed simple guidelines on the use of PET for breast cancer in the preoperative setting.

References

(Please refer to Chinese version)

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